TABLE OF CONTENTS

SUMMARY

Inspection of this medical device manufacturer was initiated by a CDRH Division of Bioresearch Monitoring Assignment #11468333, an Early Intervention – Domestic IDE-based Vulnerable Population Inspection Assignment. This inspection was conducted following Compliance Program 7348.810 under PAC 48810: Sponsors, Contract Research Organizations, and Monitors.

Previous Inspection on 5/30 to 6/26/2013 covered Medical Device Manufacturing Quality System regulations. At the time the operations were Conceptus, Inc. As of July 1, 2013 Conceptus, Inc. was acquired by Bayer Healthcare, LLC of Whippany, NJ. That inspection found no objectionable conditions, no FDA 483 was issued.

Current inspection on April 27 to May 5, and June 10 to July 1, 2015 covered Sponsor operations for clinical research in support of the Essure system for permanent birth control, (b) (4) Sponsor activities for Bayer Healthcare, LLC are centered in Whippany, NJ. Files were available locally and some were transferred to Bayer in Milpitas, CA. The inspection was interrupted after

May 5, 2015. The records for the clinical study No (b) (4) (b) (4) (b) (4) were reviewed where they were located at the Contract Research Organization. The inspection of Bayer was postponed pending an inspection of (b) (4) (b) (4) Bayer/Conceptus' CRO.

Inspection resumed and covered Files for clinical studies sponsored by Conceptus and inherited by Bayer after acquisition. These study files were stored at storage facilities in the San Francisco Bay area. The files were shipped to the Bayer Offices. Specific Investigator site files were reviewed going back to 1998.

Current labeling and Complaint data were collected.

No significant observations of current sponsor activities were observed.

ADMINISTRATIVE DATA

Inspected firm:	Bayer Healthcare LLC
Location:	1011 McCarthy Blvd Milpitas, CA 95035-7920
Phone:	(650) 962-4000
FAX:	
Mailing address:	1011 McCarthy Blvd Milpitas, CA 95035-7920
Dates of inspection:	4/27/2015, 4/28/2015, 4/29/2015, 4/30/2015, 5/1/2015, 5/4/2015, 5/5/2015, 6/10/2015, 6/11/2015, 6/12/2015, 6/15/2015, 6/16/2015, 6/17/2015, 6/18/2015, 6/24/2015, 6/25/2015, 6/26/2015, 6/30/2015
Days in the facility:	19
Participants:	Timothy C. Grome, Investigator Kristin M. Abaonza, Investigator

On April 24, 2015, I, CSO Timothy C. Grome, pre-announced the inspection to Henry V. Bishop, Senior Quality Manager. On April 27, 2015, I, CSO Timothy C. Grome, showed my credentials and issued an FDA 482 (Notice of Inspection) to G. Robert McCarthy, Senior Director of Operations. On April 30, 2015, Timothy C. Grome and Kristin M. Abaonza showed our credentials and issued an FDA 482 to G. Robert McCarthy, Senior Director of Operations. The inspection was discontinued on May 5, 2015. On June 10, 2015, I, CSO Timothy C. Grome, showed my credentials and issued an FDA 482 to G. Robert McCarthy, Senior Director of Operations.

HISTORY

In July 2013, Conceptus was acquired by Bayer Healthcare, LLC, a subsidiary of Bayer AG. At the same time the business was moved from Mountain View to Milpitas, CA. According to Henry V. Bishop the registration is current for 2015. According to Henry V. Bishop, Senior Quality Manager, when Bayer acquired Conceptus in 2013 the clinical affairs department and the marketing departments were all clinical, were absorbed by Bayer. The operations of Conceptus that stayed local to the Milpitas site are manufacturing, and Research and Development. Clinical study records collected by Conceptus as a sponsor were transferred to Bayer Healthcare in Whippany, NJ.

This location is used for Research and Development, and Manufacturing of Essure coil for permanent contraception. Complaint handling is under the purview of Global PharmacoVigilence in Germany, with satellite offices around the world including one in Whippany, NJ.

All correspondences to this site should be addressed to:
G. Robert McCarthy, Senior Director of Operations
Bayer Healthcare LLC.
1011 McCarthy Rd.
Milpitas, CA 95035

INTERSTATE COMMERCE

The Bayer Healthcare, LLC Milpitas, CA facility manufactures Essure contraceptive coils for distribution in the United States. Bayer uses manufacturing facilities(b) (4)

JURISDICTION

Conceptus, Inc. then as Bayer Healthcare, LLC sponsored clinical studies of progressive models of Essure coil for permanent contraception. Protocols are listed below. Some clinical studies were Post Approval Studies for which approved, marketed devices were used as test articles. All other clinical studies were under Investigational Device Exception (IDE). The Essure system for Permanent Birth Control is PMA P020014(b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

G. Robert McCarthy, Senior Director of Operations identified himself as the most responsible person in charge at the Milpitas facility.

The Bayer personnel supporting the inspection prepared and gave me a printout of organization charts showing the chain of command from Werner Baumann, Chief Executive Officer of Bayer HealthCare, in Berlin, Germany, through to G. Robert McCarthy, Senior Director of Operations (Exhibit #1). Bayer personnel are not given titles but are identified by their area of concern. Under Mr. Baumann is Head of Product Supply, Dr. Harmut Klusik, also in Berlin, Germany. Under Dr. Klusik is Head of Pharma, Dr. Johannes Michaelis, Berlin, Germany. Reporting to Dr. Michaelis is the head of Regional Sites & Contract Manufacturing, Dr. Reinhardt Vorreuther, Berlin, Germany. G. Robert McCarthy, Senior Director of Operations reports to Dr. Vorreuther.

A Product Supply (Milpitas Facility) organization chart printout was given to me (Exhibit #2). This chart shows:

Henry V. Bishop, Senior Quality Manager, reports to G. Robert McCarthy. Mr. Bishop was present on April 27, and on each day from June 10 through the end of the inspection. I held a close-out discussion on June 30, 2015 with Henry Bishop and G. Robert McCarthy.

Ayesh (nmi) Siddiq, Manager Medical Device Reporting, provided information on Adverse Events and product complaints. She reports to Michael Reddick, Product Surveillance, who reports to Mr. McCarthy.

The following persons traveled to Milpitas, CA from remote locations to participate in the inspection:

Andrew "Andy" (nmi) Hargreaves, Global Quality Strategist (Whippany, NJ) coordinated Bayer's inspection support team for the sponsor inspection. We was present from 4/28 to 5/5, and then from 6/25 to 6/26.

Teija M. Ternova, Senior Study Manager, (Turku, Finland) was on the Global Clinical Team, for Essure after Conceptus was acquired by Bayer. She was present at the opening meeting on April 27, 2015. She was present teach day through May 5.

Sona Grossova Garie, Line Manager for Study managers, was present on April 30, 2015, during review of (b) (4) study.

The following personnel were also present at the opening meeting:

Gerald G. Mahom, MD, Vice President of Global Development (Whippany, NJ). Dr. Mahom reports to Max Wagner, Head of Global Development TA General Medicine.

Ru-Fong J. Cheng, Global Clinical Leader, (Whippany, NJ) Ms. Cheng reports to Dr. Mahom. She is the signatory on the protocol for Study 16974 TransVaginal Ultrasound (TVU).

Eileen P. Hanna, Global Clinical Project Manager (Whippany, NJ)

Alicia A. Lowry, Assistant Director Global Regulatory Affairs

Annette H.E.F. Prelle, Head Inspection Management

Kimberly A. Rosen, Global Clinical Leader

On June 16, 2015, I held a teleconference on adverse events, complaints and signal detection. Henry V. Bishop, Senior Quality Manager, was present live and the attendees by teleconference are listed (Exhibit #3). Another teleconference was held on June 18, 2015 covering transfer of clinical studies from Conceptus to Bayer (Exhibit #4).

FIRM'S TRAINING PROGRAM

Training for Global Clinical Team members is provided and stored at the Whippany, NJ facility.

CLINICAL OPERATIONS

Clinical operations for Bayer Healthcare are located in Whippany, NJ. Because records for clinical studies sponsored by Conceptus before being acquired by Bayer were located in the San Francisco Bay Area, a records review was performed at the Milpitas, CA location. Henry V. Bishop, Senior Quality Manager gave me a list of all clinical studies conducted on behalf of the Essure product for both Conceptus, Inc. and Bayer Healthcare, LLC (Exhibit #5)

The Clinical Studies for which I reviewed records are: (b) (4) (b) (4) (b) (4) (b) (4) STOP was the original name for Essure by Conceptus.

1. Organization and Personnel

After acquisition by Bayer Healthcare, the Clinical Study operations of Bayer completely replaced that used by Conceptus, Inc. No former Conceptus, Inc. clinical affairs personnel were available for interviews during this inspection.

Clinical research at Bayer Healthcare is divided into three levels. The top level is the Global Project Team which oversees the research in support of a product line. Below that is the Global Clinical Team which runs product clinical development, developing new product applications. Below the Global Clinical Team is the Study Team which is responsible for an individual study. The study team consists of a Manager, who leads the team; a Lead Monitor, who oversees monitoring activities; a Data Manager, in charge of data management; a Medical Expert, in charge of adverse event determination, and a study statistician. For the (b) (4) study the leader of the clinical team is Ru-fang J. Cheng, Global Clinical Leader. The diagram for this arrangement was provided to me as a printout (Exhibit #6).

2. Selection and Monitoring of Clinical Investigators

Teija M. Ternova, Senior Study Manager, gave me a list of principal investigators (Exhibit #7)

Andrew Hargreaves, Global Quality Strategist, told me that the clinical investigators were selected by Conceptus, Inc. by the former company's clinical affairs personnel, under its SOPs. He provided, on 4/28/2015, me with a copy of the list of SOPs used for the (b) (4) study (Exhibit #8).

Site qualification both under Conceptus and under Bayer HealthCare was a joint effort of the Sponsor and Clinical Research. Clinical Investigators are chosen for their knowledge and experience of the Essure placement procedure. Principal Investigators are used in multiple studies over time.

I reviewed the Clinical Study Site Qualification Report for site (b) (4), (b) (6), (b) (7)(C) The Site Qualification form was completed by telephone. The form lists site and staff qualifications. I verified qualification on the form corresponded to qualifications listed in the Protocol section 3.1, Integrated Clinical Study Protocol (b) (4)
(b) (4)
23 June 2014. A full review of the records for this study was deferred to the inspection of the CRO.

I asked Teija M. Ternova, Senior Study Manager, if any investigators were disqualified and/or had studies closed down because of non-compliance. She said "No".

3. Selection of Monitors

The list of outside services for th(b) (4) was prepared at my request and is included (Exhibit #9). The list includes the contact person. According to Teija M. Ternova, Senior Study Manager, oversight of outside contractors is the responsibility of the Study Team.

Andrew Hargreaves, Global Quality Strategist gave me a list of monitors would have worked on the Essur(b) (4) study (Exhibit #10). He also gave me a copy of the Client Master Services Agreement between Conceptus and (b) (4) with revision after Bayer Healthcare LLC acquired Conceptus (Exhibit #11).

Monitoring for study(b) (4) and(b) (4) were contracted by(b) (4) (b) (4)

4. Monitoring Procedures and Activities

Apart from the Bayer Healthcare Procedures (Exhibit #8) the monitors used their own procedures. The Conceptus, Inc. procedures (Exhibit #12) were used prior to the acquisition by Bayer HealthCare LLC.

I reviewed available sponsor files. For the clinical sites that I reviewed Site initiation Visit reports recorded training of investigators and site personnel. Interim monitoring was documented by pre-monitoring and post-monitoring letters, and Interim Monitoring Visit reports.

A more thorough review of the(b) (4) study was deferred to the inspection of the CRO. Reviews of earlier studies focused on specific subjects.

5. Adverse Experience/Effects Reporting

Andrew Hargreaves, Global Quality Strategist, provided me with a memory device (Exhibit #13). The spreadshee(b) (4) MDR compiles MDR reports and Adverse Event listing from ongoing clinical trials, over the time period from October 1, 2013 to May 27, 2015. I requested records in the data formats that they were stored. Mr. Hargreaves gave me a memory device with "Let's Talk Essure Summit 2010" written on it (Exhibit #14). Stored on this device is a file "All complaints from Clinical Trials". The trials with Adverse Event data are:(b) (4) (b) (4)

Henry V. Bishop, Senior Quality Manager, provided me with the following documents:

(b) (4) study: Adverse Event information, excerpt from Final Report (Exhibit #15)

(b) (4) Adverse Event information (Exhibit #16)

In response to my inquiry about how adverse events involving coil migration were handled across clinical studies, Mr. Bishop gave me a copy of an appendix from the(b) (4) (b) (4) Appendix B: Protocol (b) (4) (b) (4) (Exhibit #17)

6. Data Collection and Handling

Data management services for the(b) (4) were subcontracted to(b) (4) (b) (4)

I asked Bayer officials present at the inspection what process analyzed adverse events for identifying trends. Andrew Hargreaves, Global Quality Strategist gave me a presentation, Essure: (b) (4) (Exhibit #18). I requested and received the Bayer HealthCare Research & Development SOP(b) (4) Version 3.0 01-Jul 2014 (Exhibit #19). The system relies on event team oversight meetings covering events.

7. Record Retention

Records of clinical studies going back to 1998 were stored offsite. Bayer was able to provide the stored files within 24 hours.

8. Automated Entry of Clinical Data

None of the studies that were reviewed used electronic Case Report Forms. Paper CRFs were manually entered into database systems online, employing electronic document controls. Document controls employed limited system access and audit trails.

9. Test Article

a. Integrity

Integrity of the test articles used in the multiple studies was by the Quality Control of the manufacturing operations, including packaging and labeling. Shipping validation is conducted under product development procedures. No investigational devices were recalled.

b. Accountability

Sponsor records reviewed for device accountability documentation were found to be complete. No unresolved accountability issues were observed in the records from any of the reviewed studies.

10. Sample Collection

No samples were collected during this inspection.

MANUFACTURING CODES

Not Applicable.

COMPLAINTS

I (CSO Grome) collected databases of product complaints from Andrew Hargreaves, Global Quality Strategist. He provided me with a memory device (Exhibit #13). That device has a spreadsheet (b) (4) listing customer complaints from 10/2/2013 to 6/10/2015. The spreadsheet (b) (4) MDR compiles MDR reports and Adverse Event listing from ongoing clinical trials, over the time period from October 1, 2013 to May 27, 2015. The spreadsheet MC Data to FDA is a complete list of product complaint reports from 12/7/2010 to 10/3/2013. I requested data tables in their original format. Mr. Hargreaves gave me another memory device (Exhibit #14) that had adverse events and complaints as listed by the different data collection systems.

RECALL PROCEDURES

Not applicable. No Investigational Devices were recalled.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

During this inspection I found no site specific objectionable conditions.

REFUSALS

No firm officials or personnel made any refusals to me during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

On June 30, 2015, I told G. Robert McCarthy, Senior Director of Operations and Henry V. Bishop, Senior Quality Manager. I said that the data reviewed were from old studies under an obsoleted

clinical management system. I had no observations. I said that even though I did not cite observations that did not mean that any existed. I warned of penalties for violation of laws enforced by FDA.

ADDITIONAL INFORMATION

Labeling

Labeling and promotional material was provided to me by Henry V. Bishop, Quality Manager, on June 11, 2015. Mr. Bishop told me that marketing material is held in Whippany, NJ. The samples that Mr. Bishop provided were delivered from Whippany. Package labeling was from packaging raw material storage at BHC, Milpitas, CA.

Design Controls

According to Henry V. Bishop, Senior Quality Manager, there have been no new completed design projects since the last inspection under Device GMPs. He provided me with a copy of the Bayer HealthCare Risk Management Procedure for Development Products SOP-03358, Rev. A (Exhibit #20), Product Development Process SOP-00799 Rev. AB (Exhibit #21), and the Design FMEA for (b) (4) Rev. C (Exhibit #22). The dFMEA (Design Failure Modes and Effects Analysis) includes the summary (pages 1-7) and the dFMEA (pages 8-17).

SAMPLES COLLECTED

Not applicable.

VOLUNTARY CORRECTIONS

There were no observations from the previous inspection to confirm corrections.

EXHIBITS COLLECTED

Documents provided to the investigators as photocopies or printouts were stamped "COPY" and had a number written in ink on it denoting the consecutive number of the request.

1. Organization charts from senior Bayer Healthcare Management to Senior Management at Bayer Healthcare, LLC Milpitas, CA. (4 pages)

2. Organization chart for Bayer Healthcare, LLC Milpitas (1 page)
3. Bayer attendees at teleconference on June 16, 2015
4. Bayer attendees at teleconference on June 18, 2015
5. List of Essure Studies (3 pages)
6. Diagram of clinical study organization hierarchy (1 page)
7. List of Investigators for Study (b) (4) (b) (4) (6 pages) Request #15
8. Current Bayer SOPs used for (b) (4) (1 page) Request #21, provided by Andrew Hargreaves on 4/28/2015.
9. Third Party Contractors for Study (b) (4) 1 page)
10. (b) (4) Monitors for (b) (4) study (1 page) Request #19.1 provided by Teija M. Ternova, Senior Study Manager on 4/27/2015
11. Client Master Services Agreement for (b) (4) signed by Conceptus, 08/23/2012, signed by Bayer HealthCare 10/20/2014 (15 pages) Request #11,
12. Clinical Study Monitoring Conceptus SOP-00531 obsolete (7 pages) Request #26 provided by Andrew Hargreaves on 4/28/2015.
13. Memory Device labeled "essure" containing Adverse Event and Complaint data (1 device)
14. Memory Device labeled "Let's Talk Essure Summit 2010" with files of adverse events collected via different database systems. (1 device)
15. (b) (4) study: Adverse Event Information (1 page)
16. (b) (4) study: Adverse Events Information (1 page)
17. Appendix B from the (b) (4) Protocol: (b) (4) (b) (4) 3 pages)
18. Essure: (b) (4) (6 pages)
19. Bayer HealthCare Research & Development SOP (b) (4) SOP-014 Version 3.0 01-Jul 2014 (16 pages)
20. Bayer HealthCare Risk Management Procedure for Development Products SOP-03358, Rev. A (18 pages)
21. Product Development Process SOP-00799 Rev. AB (17 pages)
22. Design FMEA for (b) (4) Rev. C (17 pages)

ATTACHMENTS

1. FACTS Assignment 11468333 Early Intervention – Domestic IDE-based Vulnerable Population Inspection Assignment

2. FDA 482 to G. Robert McCarthy, Senior Director of Operations April 27, 2015
3. FDA 482 to G. Robert McCarthy, Senior Director of Operations April 30, 2015
4. FDA 482 to G. Robert McCarthy, Senior Director of Operations June 10, 2015

Timothy C. Grome, Investigator

Kristin M. Abaonza, Investigator